Editorial

Update and review of conjunctival melanoma treatment

Actualización y perspectivas en el tratamiento del melanoma conjuntival

M. Satué Palacián*, E. García-Martin, FJ. Fernández Tirado, L.E. Pablo Júlvez

Servicio de Oftalmología, Hospital Universitario Miguel Servet, Instituto Aragonés de Ciencias de la Salud (IACS), Zaragoza, Spain

Conjunctival melanoma is a highly aggressive tumor with significant mortality and relapse rates despite adequate therapeutic management. The incidence of this tumor is below that of uveal and skin melanoma. It generally appears around the sixth decade of life, frequently as a black or gray nodule, usually located in the sclerocorneal limbus. It can be painless or exhibit irri-
tation symptoms.

The treatment of conjunctival melanoma continues to be complicated. Two premises must be taken into account: the first is that due to its high relapse rate it is difficult to control, even years after successfully removing the initial injury. The second premise is that due to its high metastatic potential, it is crucial to diagnose and treat conjunctival melanoma at an early stage. Even though a small percentage of these tumors can arise de novo, up to 75% of cases appear over precursor pigmented injuries (nevus and primary acquired melanosis [PAM]), which must be biopsied and studied at the microscopic level in the presence of any sign of growth.

Research in conjunctival melanoma treatment develops in small steps. The gold standard technique continues to be complete tumor exeresis. Adjuvant therapies are essential to achieve complete treatment and accordingly diminish recurrence rates. Intra-surgery, cryotherapy applied on the tumor base and edges of the lesion successfully eliminates possible macro- and microscopic remains, leaving the surgical wound free of tumor cells. Even though cryotherapy continues to be widely used, some authors consider it an obsolete technique and prefer brachytherapy with ruthenium-106 or topical mitomycin C (MMC) (for infiltrating tumors or on-site, respectively), achieving recurrence rates below those of cryotherapy.1

At present, several chemotherapy substances have demonstrated their effectiveness in post-surgery treatment of conjunctival melanoma. Mitomycin C has demonstrated good results for on-site treatment of melanoma2–4 and has been successfully applied for treating and eradicating PAM with atypia, in topical drops ranging between 0.02% and 0.04%.5 Interferon alpha 2b is another effective chemotherapy substance which is increasingly applied for adjuvant treatment of on-site conjunctival melanomas.5–7 In a dilution of 1,000,000 UI/ml, it can be topically applied several times a day for various periods of time ranging between 6 weeks and 6 months.6,7

Recent studies with cell lines present in recurring conjunctival melanoma, CRMM-1 and CRMM-2 (C: conjunctival, R: recurring, MM: malign melanoma) have demonstrated sensitivity to certain cytotoxic substances, enabling the possibility of new combination therapies. Mitomycin C, as well as cis-
platin, a chemotherapy drug utilized in sarcomas and ovarian tumors, has demonstrated antitumor effects inhibiting the growth of cell lines present in conjunctival melanoma. The combination of trans-retinoic acid with mitomycin C or with imatinib (tyrosine kinase inhibitor) has demonstrated synergistic effects to inhibit the CRMM-2 cell type. In addition, the combination of mitomycin C with imatinib increases

---


* Corresponding author.
E-mail address: mariasatue@gmail.com (M. Satué Palacián).

2173-5794/$ – see front matter © 2013 Sociedad Española de Oftalmología. Published by Elsevier España, S.L. All rights reserved.
its efficacy, which could be very useful for considering new treatment guidelines. The most recent study by Westekemper et al. could open new possibilities for the treatment of this recurring melanoma by means of the application of chemotherapy drugs which are not widely applied and have never been used in ophthalmology: ranpirnase, a ribonuclease from *pipiens* frogs, which until now has been used in the treatment of pleural mesothelioma and has obtained approval in Europe even though it is not yet designated in the United States and Australia (i.e., it is focused on the treatment of rare diseases and is not marketed due to lack of profitability). Additional rarely used chemotherapy drugs include bortezomib (proteosome inhibitor) or nemorosone, a polyclyclic acylphuguroglucinol and natural polyphenylate which acts on the membrane potential of mitochondria and adenosin triphosphate (ATP) of the cancer cell lines that have been studied. Said new chemotherapy drugs could become a good alternative to known local therapies.

However, there is no evidence that topical chemotherapy drugs are also effective for infiltrating melanoma where iodine-125 in brachytherapy or ruthenium-106 could be the best therapeutic option in early stages. A series of 19 cases published in 1911 by Karim and Conway utilized iodine-125 at a dose of 100 Gy injected at a depth of 1.5–3 mm, after performing conservative tumor surgery. No recurrences were recorded during the follow-up period (43 months) and only 3 patients exhibited new tomorrow lesions far from the site of the main lesion.

Conjunctival melanoma prognosis worsens with recurrence as it involves a significant increase in the risk of remote dissemination. Additional factors increasing the risk of metastasis is the involvement of the palpebral conjunctiva, a tumor thickness above 0.5 mm, invasion in depth or locoregional ganglionary invasion. The lymphatic drainage of the ocular surface is one of the main enemies for treating conjunctival melanoma as it has proven to be more complicated than the well accepted sub-maxillary-preciliary drainage. Studies with primates have demonstrated that this circulation is effected through the submaxillary and parotid ganglions from different conjunctival areas. The study of the parotid gland has been questioned as staging protocol. However, series such as that of Vira et al. recommend studying said gland when suspecting lymphatic dissemination of the tumor. The usefulness of the sentinel ganglion in conjunctival melanoma has also been questioned because, due to the highly complicated lymphatic conjunctiva anatomy and the presence of metastasis without obvious ganglionary involvement, the study of the sentinel ganglion does not appear to have a significant impact in survival rates or types of treatment. Unfortunately and despite adequate management of these tumors, relapse rates remain high, reaching 45% in 5 years according to some series, with a mean recurrence period of 14 months and an overall mortality rate of 25% at 10 years.

To conclude, recent developments in the treatment of superficial melanoma have focused on chemotherapy drugs and have the main purpose of eliminating the tumor in the preinvasive stage and prevent recurrence. New combinations of these drugs could involve significant progress toward controlling the disease. However, the aggressiveness and high relapse and dissemination rates of conjunctival melanoma continues to be a significant problem, with numerous studies reminding us of the importance of finding new specific drugs to prevent the appearance of distant metastasis. At this date, early diagnosis continues to be the main weapon for addressing this type of tumor (Fig. 1).

**Fig. 1 – Patient with melanoma on-site over primary acquired melanosis (PAM) with atypia in the superior tharsal conjunctiva.**

**References**


